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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,881	03/22/2004	Ibert C. Wells	800812-0005	9725

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,881	WELLS, IBERT C.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,19 and 36-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,19 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/07, 1/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received November 11, 2007 are acknowledged.

Claims 2, 5, 7-18, and 20-35 have been canceled.

Claims 1, 19, and 36 have been amended.

Claims 1, 3, 4, 6, 19, and 36-40 are pending in the instant application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3, 4, 6, 19 and 36-40 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record.

The office action mailed May 15, 2007 states:

> As has been previously stated, applicant has claimed an assay wherein levels of the peptides of SEQ ID NOs:1 or 4 are measured in patient samples, with detection of lower than normal levels of said peptides being indicative of preeclampsia. SEQ ID NO:1 is the polypeptide sequence FFGLM while SEQ ID NO:4 is the sequence FXGLM, wherein X is either F or V. These polypeptide sequences are found in the C-terminal end of all mammalian tachykinins (see paragraph 18 of the instant specification). Tachykinins are a diverse family of small endogenous polypeptides that participate in numerous physiological processes, with the sequence FFGLM occurring in substance P and the sequence FVGLM (one of the two possibilities for SEQ ID NO:4) being found in neurokinin A and neurokinin B (see Table 2 of Pennefather et al.).
> To support applicant's hypothesis that lower than normal levels of SEQ ID NOs:1 and 4 are correlated with the disease preeclampsia, applicant has disclosed the following data.
>
> The specification discloses that red blood cell membranes from patients with hypertension (Examples 1 and 8), diabetes (Example 8), and preeclampsia (example 4) comprise less bound magnesium than what is found in normal controls. Applicant has characterized this apparent deficiency in bound magnesium as the "magnesium binding defect (MBD)" Applicant has also disclosed that adding SEQ ID NO:1 to red blood cells deficient in magnesium caused the cells to bind additional magnesium, yet addition of SEQ ID NO:1 to normal red blood cells does not lead to increased magnesium binding (Examples 3 and 7). The specification does not disclose that SEQ ID NOs:1 or 4 were ever measured in samples obtained from patients suffering from hypertension, diabetes, or preeclampsia. The specification also does not

disclose data demonstrating that the removal of SEQ ID NOs:1 or 4 causes MBD either in vivo or in vitro. Note that Example 6 discloses a protocol for artificially inducing MBD in red blood cells in vitro, but this protocol does not appear to comprise the peptides of SEQ ID NOs:1 or 4.

As such, the hypothesis upon which applicant's claimed method is based, i.e. that lower than normal levels of the peptides of SEQ ID NOs: 1 and 4 are found in women with or at risk of developing preeclampsia, has not been experimentally verified. The rejections of record have discussed how Sanfilippo et al. observed that the level of substance P in the amniotic fluid of diabetic patients is increased relative to controls, while Page et al. disclose that the plasma level of neurokinin B in patients diagnosed with preeclampsia was significantly increased as compared to normal controls (both of record). Note that the observations of Page et al. that plasma levels of neurokinin B are elevated as compared to normal in preeclampsia have been confirmed by D'Anna et al. (BJOG, 2004, 111:1046-1050, see entire document, particularly the abstract). Applicant has previously argued that the teachings of Sanfilippo et al. and Page et al. are not pertinent to the claimed invention because their assays measure the full length tachykinin polypeptide and do not measure breakdown products (i.e. they did not measure the polypeptides consisting of SEQ ID NOs:1 and 4). While the previous claims were limited to measuring the levels of peptides consisting of SEQ ID NOs: 1 and 4, a limitation not present in the teachings of Sanfilippo et al. or Page et al., no reasonable explanation was set forth as to why a skilled artisan would expect in the instant circumstance that the concentration of a breakdown product decreases (SEQ ID NOs:1 and 4) while the concentration of the native product (substance P, NKB) increases.

Given that applicant has not explicitly demonstrated the link between peptide levels and preeclampsia, and the teachings of the art that the precursors of the peptides recited in the instant claims increase, rather than decrease, in preeclampsia, a skilled artisan would not reasonably conclude that applicant's claimed invention would be diagnostic for preeclampsia based on the evidence provided in the instant specification. Therefore a skilled artisan would be unable to use the claimed invention.

Applicant's arguments filed February 22, 2007 have been fully considered but they are not persuasive. Applicant repeats arguments already of record that "the specification provides evidence demonstrating that levels of peptides of SEQ ID NOs: 1 and 4 directly correlate with the presence of the magnesium binding defect." Applicant's supports this argument by stating that the prior art established that an unknown component of normal rat serum corrects the MBD seen in a hypertensive rat model, and that the instant specification demonstrates that by adding the peptide consisting of SEQ ID NO:1 to red blood cells the MDB can be corrected. From these observations, applicant concludes that low serum concentrations of the peptides of SEQ ID NO:1 and 4 must be present to observe the MBD. Indeed, applicant explicitly states in the response:

> "The above conclusion is based on the following: 1) Normal serum levels of Peptides are presumed present in normotensive rats which do not have the magnesium binding defect; and 2) administration of Peptides to hypertensive rats increases the serum levels of Peptides. As such, we know that the serum levels of Peptides were lower when the magnesium binding defect was observed, and the levels were higher after administration of Peptides when magnesium binding increased to normal levels in the hypertensive rats."

This argument is not persuasive because applicant's logic is flawed. Applicant states that "we know that the serum levels of Peptides were lower when the magnesium binding defect was observed". This is true because the final concentration of Peptides must be greater than the initial concentration, the difference being the amount of added Peptides. What is not stated is the assumption that the initial concentration of Peptides is lower than normal in the hypertensive rats, and that therefore lower than normal concentrations of the peptides consisting of SEQ ID NOs:1 and 4 is responsible for the MBD. No direct evidence, such as measuring the level of the peptides consisting of SEQ ID NOs:1 and 4, has been provided. Applicant's entire invention is based upon this assumption. The following analogy may help to elucidate why such an assumption is not necessarily true.

It is known in the art that lymphoma, like all types of cancer, are characterized by excessive cellular proliferation. It is also known that IL2 is an endogenous cytokine that when added to lymphocytes, including lymphomas, causes cellular proliferation (Duprez et al., PNAS 1985, 82:6932-6936, see entire document, particularly the abstract). Using applicant's logic, a skilled artisan would thus be able to diagnose lymphoma if greater than normal levels of IL2 are measured in a patient sample. Unfortunately, this is not true. Mainou-Fowler et al. disclose that samples from lymphoma patients actually comprise less IL2 than normal controls (Leuk. Lymphoma, 2003, 44:13254-31, see entire document particularly the abstract). As such, hypotheses must be tested before being accepted as true.

There are many potential causes for why red blood cells may lack a normal level of magnesium on their plasma membranes, including such things as inadequate dietary ingestion of magnesium. The instant specification has defined MBD such that it excludes nutritional deficiencies (see paragraph 26) but given the numerous and diverse roles magnesium plays in the body such as in the formation of ATP, as an enzymatic cofactor, and as an intracellular messenger, it seems likely that the body has multiple pathways which act to control magnesium levels (Romani et al., Frontiers in Bioscience, 2000, 5:720-734, see entire document). The factor(s) present in normal rat serum that ameliorated the MBD in the prior art were never identified, nor was hypertensive rat serum tested for the presence of the peptides consisting of SEQ ID NOs:1 and 4. The fact that addition of SEQ ID NO:1 allows more magnesium to bind cells characterized by the MBD but does not affect normal cells is not convincing evidence that there was less than the normal concentration of SEQ ID NO:1 in the in vivo environment of the MBD cells. For example, a characteristic of Type II diabetes is insulin resistance. In insulin resistance, the patient's cells become refractory to the uptake of glucose even in the presence of ever increasing physiological concentrations of insulin that are being produced by the patient. Many of these patients can have their diabetes successfully controlled by the administration of exogenous insulin (Carver C, see entire document). As such, the level of insulin in the type II diabetic patient is higher than in a normal person, yet the disease is effectively treated by increasing the concentration of insulin even further above normal physiological levels. As such, the observation that more of something causes an effect is not evidence that the something was initially present at a lower than normal concentration.

The examiner is not aware of any data, either in the instant specification, declarations submitted by applicant , the prior art, or post-filing date art, wherein the peptides consisting of SEQ ID NOs:1 or 4 were measured and observed to correlate with a lack of cellular membrane bound magnesium. Note that the presence of such data would amount to no more than reducing the instant claimed method to practice. Given the issues discussed above, and the central importance of a direct correlation between low peptide levels and the MBD, a skilled artisan would not reasonably conclude that applicant's invention would work in the absence of additional data concerning the actual measurement of the peptides consisting of SEQ ID NOs:1 and 4.

Additionally, it is noted that applicant has amended the independent claims to recite "consist essentially of" rather than "consists of" the recited biological sequences. The meaning of the term "comprising" in relation to biological sequences is open, such that additional sequence may be added to either or both ends of the recited sequence. The term "consisting of" is closed, such that the claim is limited to the exact recited sequence without any additions. The term "consisting essentially of" is generally interpreted as being "open", unless the specification defines the phrase differently or it can be shown that the additional sequence materially affects the basic characteristics of the recited sequence. In the instant application, there is does not appear to be guidance in the specification concerning how "consisting essentially of" is to be interpreted. Given the experimental data provided in Table 5 of example 7 of the instant specification that both substance P and the peptide consisting of SEQ ID NO:1 promote the binding of magnesium to cells, it does not appear that additional polypeptide sequence can reasonably be said to materially affect the properties of the peptides recited in the instant claims. As such, the phrase "consisting essentially of" has been interpreted to be equivalent with "comprising" for the analysis of the instant claimed invention. As discussed above, Sanfilippo et al. specifically measured substance P in a body fluid from pregnant women and observed that higher than normal levels of substance P were found in women with diabetes as compared to normal controls. Page et al. measured NKB and observed that women with preeclampsia had an increased level of NKB as compared to controls. Note that the specification teaches that hypertension, diabetes and preeclampsia have a common marker, the presence of the MBD (paragraph 24), and that "the results reported herein provide circumstantial evidence that the individual experiencing preeclampsia is in the prediabetic phase of type 2 diabetes mellitus, the stage prior to overt type 2 diabetes. This indicates that commonly experienced preeclampsia results from the imposition of pregnancy on type 2 prediabetes mellitus." (paragraph 55). Therefore, the data of Sanfilippo et al. and Page et al., which measured polypeptides which comprise SEQ ID NOs:1 and 4 appear to indicate that applicant's claimed method will not work because the polypeptides are increased, rather than decreased in women afflicted with preeclampsia.

The rejection is maintained.

Applicant's arguments filed November 15, 2007 have been fully considered but they are not persuasive. Applicant repeats arguments previously presented concerning

why the specification indicates that the claimed method would work, argues that the claims have been limited to measuring peptides consisting of SEQ ID NO:1 or SEQ ID NO:4, argues that a skilled artisan would known that the level of Peptides (i.e. SEQ ID NOs:1 and 4) can vary either directly or indirectly with the concentration of their precursors (i.e. substance P and NKB which are taught in the art as increasing), and that therefore the disclosure demonstrates that the method actually works and provides more than a respectable guess as to the likelihood of its operability.

This argument is not persuasive. The rejection of record discusses at length why the data disclosed in the instant specification does not reasonably demonstrate that low levels of Peptides as compared to normal controls are necessarily present in the recited patient population, and these reasons will not be discussed further. Arguments that the concentration of breakdown products (i.e. SEQ ID NOs:1 and 4) may vary directly or indirectly with the starting product does not provide data or evidence that lower than physiologically normal levels of the recited peptides are present in the recited patient population. Note that the claimed method will not work if preeclampsia patients do not have lower than physiologically normal levels of Peptides and there is no evidence in the specification, in a declaration, or in the art that women with preeclampsia have lower than normal levels of the peptides consisting of SEQ ID NO:1 and SEQ ID NO:4. Thus, based upon all of the factors discussed at length in the rejection of record, it does not appear reasonable that applicant's claimed method will work as claimed and therefore the rejection is maintained.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. The rejection of claims 36 and 37 under 35 U.S.C. 102(a) as being anticipated by Page et al. (Nature, June 15, 2000, of record, see entire document) has been withdrawn in view of applicant's claim amendments received November 15, 2007.

Specifically, the claims as amended recite closed sequence language wherein peptides consisting of SEQ ID NOs:1 and 4 are measured. The prior art discloses measuring peptides comprising the recited sequences with antibodies, but the antibodies were specific for neurokinin B, a longer sequence that comprises SEQ ID NO:4. Note that said antibodies did not bind an epitope consisting of SEQ ID NO:4.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 36, 37, 38, and 40 under 35 U.S.C. 103(a) as being unpatentable over Page et al. (Nature, June 15, 2000, of record, see entire document) in view of Janeway et al. (Immunobiology, 1997, pages 2:8-2:10 and 2:16-2:18) has been withdrawn in view of applicant's claim amendments received November 15, 2007.

Specifically, the claims as amended recite closed sequence language, a limitation not present in the art of record as discussed above.

8. No claims are allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1644